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Stress Ulcer Disease in the Burned Patient

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Stress-induced ulcers of the stomach and duodenum in massively burned patients, otherwise known as Curling's ulcers, result from a defect in the mucosal barrier to secreted acid. The etiology of this defect is related, at least in part, to mucosal ischemia, which is aggravated by hypotension, sepsis, and hypoxia. Early prophylactic administration of antacids and cimetidine, either singly or in combination, has significantly reduced the occurrence of the life-threatening complications of these lesions. When preventive measures have failed or have not been utilized and massive bleeding or perforation has occurred, these complications of Curling's ulcer appear to be best treated by gastric resection combined with vagotomy.

The stress caused by an extensive burn exceeds that associated with any other injury and exerts pervasive systemic effects involving every organ system. The initial organ response, its extent, and its duration are proportional to the extent of the burn and does not subside until the burns have healed or have been grafted and convalescence begins. The postburn changes in the gastrointestinal tract are a stereotyped response of that organ system to any injury, but are quantitatively more pronounced as a reflection of the severity of stress in the burn patient. Until recent years, the incidence of clinically significant complications of stress ulcers in burn patients exceeded that encountered in any other group of injured patients except those with brain injury.

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Characteristics of Acute Postburn Upper Gastrointestinal Ulcers

The association of acute upper gastrointestinal tract disease with burn injury was noted as early as 1823 by both Cumin [1] and Swan [2], but was largely ignored until Curling [3], in 1842, described acute duodenal ulceration in 10 extensively burned patients. Since then, such ulcers have been called Curling's ulcers. The effective early resuscitation of extensively burned patients developed in the 1940's led not only to improved survival but also to increased duration of survival, and served to highlight late-appearing complications. Consequently, the incidence of Curling's ulcers diagnosed clinically and at autopsy increased markedly, rising to over 21% in the burn patients cared for at this Institute in 1962 [4].

As recently as the early 1970's, the diagnosis of Curling's ulcer was first made at autopsy examination in 23% of burn patients with that disease [5]. The most common presenting sign was gastrointestinal hemorrhage, which occurred in 64% of patients with Curling's ulcer. Hematemesis was 2.3 times more frequent than melena. Massive hemorrhage (a decrease in the hematocrit of more than 10) or shock was the presenting sign in 43% of patients with Curling's ulcer. Unexplained distension occurred in 9% of patients, but appeared to reflect the ileus frequently associated with sepsis rather than the ulcer per se, unless the ulcer had perforated. Perforation occurred in 12% of patients. Pain was an uncommon presenting sign, occurring in only 4% of patients, and usually accompanied perforation or exsanguinating hemorrhage. The difficulty in eval-

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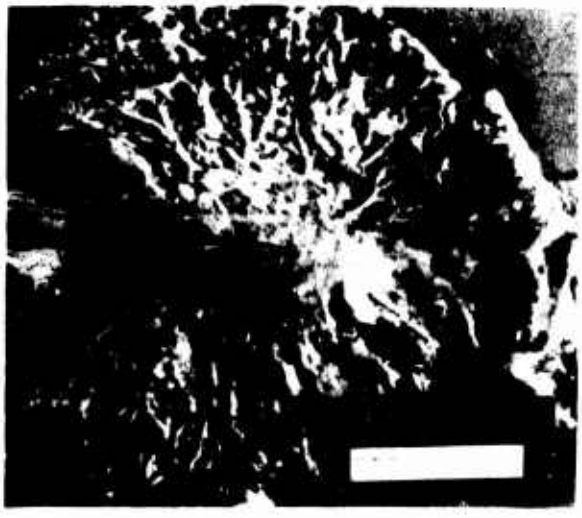

Fig. 1. Autopsy specimen obtained from patient who died with severe pneumonia 12 days following a 23% burn and associated inhalation injury, illustrating the pattern of generalized mucosal petechial change, rugal fold pallor, and multiple nodular areas of hemorrhage on rugae. Note (arrow) linear hemorrhagic erosions extending distally from esophagogastric junction, indicative of nasogastric tube mechanical trauma. Note also multiple shallow, rounded, sharply demarcated ulcerations of mucosa of antrum and pylorus.

Fig. 2. Photomicrograph of acute gastric ulcer found at autopsy in patient with 33% burn who died with severe pneumonia and empyema and had undergone previous plication of bleeding gastric ulcers. The ulcer has penetrated through much of the muscularis mucosae (arrow) and the base, on the left side of the photo, is covered with a fibrinous exudate containing few inflammatory cells. Note intact gastric glands, on the right side of photo, with no edema and virtual absence of inflammation.

uating the findings of abdominal examination in septic, often obtunded patients with burns of the abdominal wall is indicated by the fact that pain was the presenting sign in only 1/3 of those patients in whom perforation had occurred. X-ray studies of the upper gastrointestinal tract have been unreliable in diagnosing these acute lesions because stress ulcers are usually superficial in character with little edema present in the mucosal margins of the ulcerations.

Postburn upper gastrointestinal tract stress ulcers most commonly involve the gastric mucosa. These ulcers are predominantly multiple, round in configuration, and usually less than 2 cm in greatest diameter (Fig. 1), although they can be solitary, irregular in outline, and of large size. Ulcers of the duodenum, on the other hand, are usually solitary, but they too can be multiple. The lesions are characteristically shallow, involve the mucosa, and only infrequently penetrate below the muscularis (Fig. 2). The typical lesion has sharply demarcated margins showing little inflammatory change or edema. The mucosa of the fundus of the stomach is most commonly affected, but antral ulcers are not rare. In 15% of patients with Curling's ulcer, both gastric and duodenal lesions are present, a fact of importance if surgical intervention is required. Although the predominant site of stress ulcers in burned children has been reported to be the duodenum, the lesions in pediatric burn patients cared for at this Institute have been predominantly gastric in location, as is the case in adults.

The majority of our patients who have developed stress ulcers have been males; this reflects only the predominance of males in our patient population and not any sex predilection. The occurrence of frank ulceration increases as burn size increases, rising to an incidence of approximately 40% in patients with burns of 70% to 90% of the total body surface. In the course of our early studies, sepsis was identified as an important factor in the development of the clinical complications of stress ulcers in the overall burn population. The true significance of sepsis was apparent only when patients were stratified according to burn size. In those patients with sepsis and burns of more than 50% of the body surface, the incidence of Curling's ulcer was greater, but not significantly so, than in uninfected patients with similar-sized burns, presumably because the stress of the burn per se was sufficient to cause acute upper gastrointestinal ulceration. However, in those patients with burns of less than 50% of the total body surface, sepsis significantly increased the frequency of acute ulceration, presumably by accentuating overall stress. In burned children the effect of sepsis was particularly evident. The occurrence of acute gastrointestinal ulceration in this age group decreased coincident with the reduction of invasive burn wound sepsis effected by the use of topical chemotherapy. The importance of sepsis is further emphasized by the clinical observation that

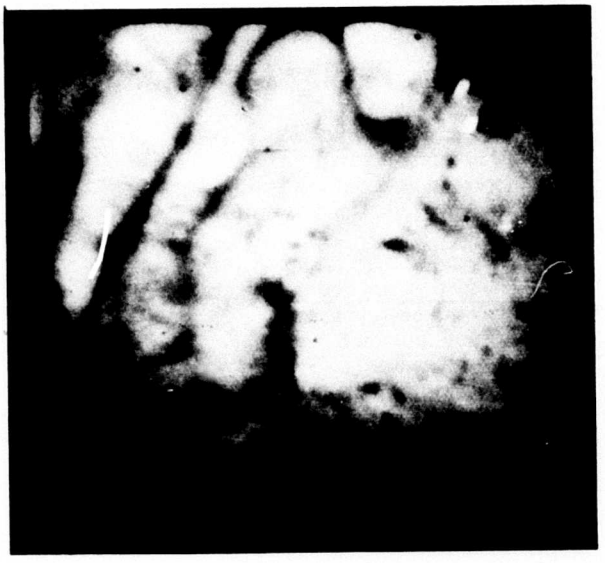

Fig. 3. Endoscopic view of gastric mucosa during resuscitation period (< 72 hours postburn). Note general pallor of mucosa upon which focal areas of hemorrhagic change and erosions of variable size and configuration are superimposed.

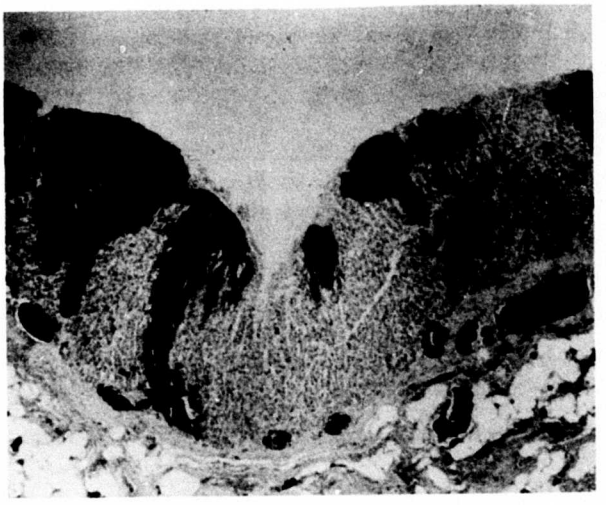

Fig. 4. Photomicrograph of autopsy tissue sample obtained from a patient who died with severe pneumonia following burns of 40% of the total body surface, showing congestion of both submucosal and mucosal vessels and multiple focal areas of hemorrhagic gastritis. Note variable extent, depth, and severity of mucosal hemorrhages as well as their generally wedge-shaped configuration.

bleeding from a Curling's ulcer has often stopped when coexisting sepsis in a burned child has been controlled [6].

Natural History of Postburn Gastroduodenal Mucosal Disease

In recent years, studies by Czaja and McAlhany [7] have defined the natural history of mucosal changes in the upper gastrointestinal tract following burn injury. Serial fiberoptic gastroduodenoscopic examinations, with the initial examination performed within 72 hours of the time of burning, revealed that the frequencies of gastritic and duodenitic mucosal changes were related to burn size. Alterations were not observed in patients with burns of less than 35% of the body surface, but were noted in 86% of patients with more extensive burns. Gastritic changes consisting of erythematous macular lesions superimposed on a usually pale mucosa, focal mucosal hemorrhage, and superficial erosions were observed as early as 5 hours postburn in 76% of 32 patients. Individual patients showed the full panoply of mucosal disease by the end of the first post burn day (Fig. 3). The mucosa of the fundus and body of the stomach was most commonly involved, but the mucosa of the antrum was involved in nearly half of the study patients. Even though ileus was present in the early postburn period in virtually all the patients and bile reflux into the stomach was observed in many, the antral mucosal changes appeared to be less pronounced and to resolve more rapidly than those in the proximal stomach. Similar mucosal changes were observed in the duodenum in 72% of patients. Histologic examination of mucosal biopsy

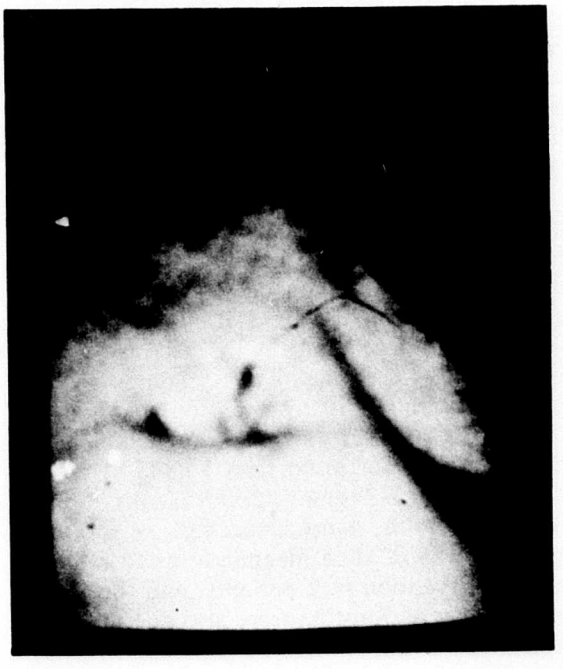

Fig. 5. Endoscopic view of gastric ulceration present at 96 hours postburn in an area showing focal gastritis (punctate areas of gray discoloration). Note absence of inflammatory change in the ulcer itself and the minimal amount of edema in the mucosa at the margin of the ulcer.

Table 1. Association of gastric and duodenal mucosal disease in burn patients, as determined endoscopically.

	Gastric disease study	Duodenal disease study
Total number of patients	54	37
Gastritis	45	18
Duodenitis	34	15
Acute gastric ulcer	14	6
Duodenal ulcer*	2	12*
Hemorrhage from erosion	5	1
Hemorrhage from ulcer	1	5
Perforation	1†	1
Patients requiring operation	1	2

*One patient had reactivation of chronic duodenal disease
†Diagnosed postmortem

Table 2. Etiologic factors in stress ulceration in burn patients.

I. Initial injury:
   Mucosal Ischemia
II. Factors causing progression:
   1. Intraluminal acid
   2. Increased acid back-diffusion
   3. Duodenal reflux of bile salts and lysolecithin
   4. Sepsis
   5. Nasogastric tube trauma
   6. Decrease in sulfated muco-substances
   7. Impaired energy supply, e.g., starvation or inadequate nutrition
III. Protective factors
   1. Mucous production
   2. Mucosal proliferation
   3. Maintenance of mucosal energy supply
   4. Carbonic anhydrase

specimens revealed microvascular congestion, edema, mucosal hemorrhage, epithelial cell necrosis superficial to the muscularis mucosae, and in some samples mild inflammatory changes (Fig. 4). In duodenal biopsy specimens, Brunner gland dilatation was occasionally noted as early as 5 days postburn.

The natural history of mucosal lesions of the stomach or duodenum appeared to be related to the patient's general condition. The majority of patients had an uncomplicated course, the lesions slowly resolved and the mucosa regained a normal appearance. In 47% of study patients, progression of the mucosal disease, manifested by either an increased number of superficial mucosal lesions or ulcer formation, was evident at the time of subsequent endoscopic examination. Frank gastric or duodenal ulceration was first evident at 96 hours postinjury, and ulcers were located in areas of intense mucosal disease (Fig. 5). In general, the disease progressed in those patients experiencing clinical deterioration in association with sepsis, hypotension, and hypoxemia. In 7 patients (22%) significant hemorrhage (defined as a need for more than 3 units of blood transfusion during a 24-hour period) occurred, and in 2 patients (6%) the acute ulcerations perforated. Hemorrhage was of such magnitude as to require operative intervention in 2 patients, and the 2 patients with ulcer perforation were also operated upon, an overall operative rate of 13% in the 32 study patients.

The results of subsequent endoscopic studies of both gastric and duodenal mucosal changes on burn patients are detailed in Table 1 [8, 9]. Duodenal ulceration occurred in 12 patients, all of whom had burns of over 42% of the total body surface. In 3 patients, areas of early mucosal slough, which appeared to be incipient ulcerations, showed infarction necrosis on histologic examination. The lesions of each of these 3 patients evolved into frank ulcers during the second postburn week, and one of these ultimately perforated. Six ulcers involved the anterior duodenal wall and 6 the posterior wall. Hemorrhage, which occurred in 6 of the 27 patients with duodenal disease, arose from an ulcer in 5 and from multiple erosions in the sixth. Bleeding occurred from 4 of the 6 posterior ulcers, but from only 1 of the 6 anterior ulcers. Septicemia, shock, or hypoxemia preceded the appearance of bleeding in all patients. One patient required surgery for control of bleeding and 1 required closure of a perforation. In the latter patient, a more distal duodenal ulceration was noted at the time of endoscopic examination 8 days after oversewing of the perforation. The majority of these patients, as in the earlier study, had an uneventful postburn course.

Etiologic Factors

Multiple etiologic factors have been implicated in the pathogenesis of stress ulcers in burn patients, but no one factor appears invariably capable of producing frank ulceration (Table 2). As is true in chronic ulcer disease, the adage "no acid, no ulcer" applies to stress ulcerations. Studies in 34 patients, using the technique of 2-hour timed gastric aspirate collection, have shown that although acid output was not predictive of acute gastroduodenal disease after burn injury, the severity of disease increased in relation to gastric acid production [10]. Acute duodenal ulcers were not identified in patients with acid secretion rates of less than 3.11 mEq/hr. The relationship of total titratable timed acid output to severity of gastroduodenal disease is illustrated in Table 3. Hemorrhage occurred in 5 of the 9 patients with duodenal ulcer, in 1 of the 15 patients with gastric ulceration, and in 2 of the 16 patients with diffuse gastritis. The patients in whom bleeding and

Table 3. Relationship of timed gastric acid production to severity of postburn gastroduodenal mucosal disease in 34 patients with burns.

	Number of patients	Mean age (years)	Mean extent of burn (% of total body surface)	Mean total acid output (mEq/hr)
No Complications	25	32	65	3.09
Normal mucosa	3	29	61	1.42
Mucosal disease	22	32	65	3.32
Complications	9	29	53	5.37
Hemorrhage	8	31	52	5.22
Perforation	1	18	64	6.56

perforation occurred were similar in regard to age and burn size to those without these complications, but the total titratable timed acid output in the former was significantly greater than in the latter.

In further studies of patients with postburn gastric disease, biopsies were obtained from areas of gastritis and adjacent intact mucosa [9]. Laboratory assessment of coagulation factors and measurement of serum protein levels were also carried out in these patients. No microvascular thrombi were identified in biopsy samples, even from those 5 patients with laboratory evidence of disseminated intravascular coagulation. In general, burn patients with both normal and diseased mucosa had low serum protein levels, but the group with acute gastritis had significantly lower protein levels (4.48 g/dl) than those with normal mucosa (5.72 g/dl), independent of burn size. It appears likely that the lower protein levels in the former group represent the effect of other complications that occurred in these patients or of exudation of protein from the injured mucosa per se, rather than a cause of the mucosal changes. Although a nasogastric tube can cause focal mucosal injury, and linear hemorrhagic erosions are often observed at the sites where such a tube has been in contact with the gastric wall, 7 of these patients were examined prior to intubation, and 4 had diffuse superficial mucosal disease of the fundus and body of the stomach, as previously described.

A recent study [11] has examined the relationship of gastric acid production and acute gastroduodenal mucosal disease, as defined endoscopically, to serum gastrin levels in 32 patients with burns of 40% to 91% of the body surface. Gastrin levels were not predictive of the occurrence, severity, or location of acute gastroduodenal disease. Gastric acidity again showed significant correlation with the severity of mucosal damage. Although there was no significant difference in gastrin levels between those patients with and those without acute gastroduodenal disease, a normal gastrin and gastric acidity relationship appeared to be preserved, with average serum gastrin levels lowest in those patients with the highest acid output per hour.

The role of pepsin secretion in stress ulcer formation in burn patients has received scant attention, even though changes in pepsinogen levels are considered to reflect secretory activity and morphologic status of the gastric mucosa in a variety of disease states. Serum samples obtained from 14 burn patients showed elevation of pepsinogen (PG-1 as determined by immunochemical means) in 2 patients, in only 1 of whom was the elevation associated with gastroduodenal hemorrhage. Moreover, pepsinogen levels showed no consistent relationship to the presence or severity of gastroduodenal mucosal disease [12].

The role of gastric mucus in the genesis of acute stress ulceration is uncertain. Gastric mucus is considered to exert a protective effect on the gastric mucosa, and a reduction in the amount or change in composition of gastric mucus presumably could predispose the burn patient to mucosal injury. O'Neill et al. [13] have shown in animal models that gastric mucus content and gastric mucus secretion rates decrease following burn injury. However, McAlhany et al. [14], on the basis of histochemical studies of gastric mucosal biopsy specimens obtained from burn patients, found gastric mucus content to be normal even in patients with acute mucosal disease. However, a depletion of sulfated mucosubstances in chief cells was a consistent finding. The observed depletion may reflect either prior response to increased pepsin neutralization or diminished cellular production, either of which would render the already impaired mucosa susceptible to further injury by pepsin.

The gastric mucosa is considered to serve as a barrier limiting the back-diffusion of hydrogen ion and defending the stomach against the deleterious effects of intraluminal acid. Disruption of the gastric mucosal barrier has been reported to occur in critically ill patients, with a resultant increase in permeability of the gastric mucosa to hydrogen ion back-diffusion. This pathologic change has been considered by some to be responsible for progressive mucosal damage and the occurrence of stress

ulcerations. The relationship between gastric mucosal barrier disruption and acute gastric mucosal disease following thermal injury was studied in 18 adult patients with burns involving 25% or more of the total body surface [15]. In 10 of the patients, the gastric mucosal barrier to acid, as assessed by a lithium flux technique, appeared to be intact, even though 7 of the 10 patients showed acute gastric mucosal lesions at the time of endoscopic examination. The remaining 8 patients were found to have disruption of the gastric mucosal barrier within 72 hours following burn injury, but only 6 of those patients demonstrated acute gastritis at the time of initial endoscopic examination. In 7 of these 8 patients, disruption of the gastric mucosal barrier was associated with subsequent mucosal bleeding, gastric ulcer perforation, or endoscopic progression of the gastric mucosal disease. In the 10 patients with a normal gastric mucosal barrier measured within the first 3 days postburn, endoscopic progression occurred in only 2. These findings indicate that in burn patients disruption of the gastric mucosal barrier with increased back-diffusion of hydrogen ion is not necessary for the development of early post-injury gastritis. However, the association of gastric mucosal barrier disruption with endoscopic and clinical progression of the early mucosal disease suggests that increased hydrogen ion back-diffusion may play a contributory role in the progression of the disease or may reflect the severity of mucosal damage and thereby serve as a clinically useful prognostic index.

The reparative capacity of the gastric mucosa following thermal injury was determined in 23 burn patients with burns involving more than 35% of their total body surface [16]. Endoscopic examination of the stomach and duodenum was carried out on the third postburn day and repeated on the 14th postburn day in each patient, and mucosal biopsies were obtained during each endoscopic examination from an area adjacent to identified mucosal lesions in both the corpus and the antrum of the stomach in each patient. The mucosal proliferative index was determined by an audioradiographic technique in 262 mucosal biopsy specimens obtained from the 23 patients. The mucosal proliferative index was elevated in all patients, with the elevation being greater in those patients with gastric mucosal disease than in those patients without mucosal disease. On the third postburn day, the proliferative index of the antral mucosa was consistently lower than the proliferative index of the fundal mucosa.

At the time of reexamination on the 14th postburn day, 4 patterns of mucosal proliferative index activity were apparent, depending upon the status of mucosa vis-à-vis its status at the time of initial examination. The mucosal proliferative index decreased to normal in those patients with a normal mucosa which remained normal; decreased (in some to normal levels) in those patients with initial mucosal changes which had healed; remained elevated or further increased in those patients with initial mucosal changes which had persisted or increased; and decreased markedly in those patients in whom mucosal disease progressed in accompaniment with clinical deterioration manifested by septicemia, hypotension, or hypoxemia. The findings in the latter group indicate that those patients who experience clinical deterioration not only have progression in the severity of mucosal disease, which may produce frank ulceration, but also have diminished capacity for spontaneous mucosal regeneration and repair.

The early appearance of gastritis and duodenitis and their morphologic and histologic characteristics point to impaired mucosal blood flow and focal ischemia as a central factor in the pathogenesis of postburn stress ulcers. The early postburn hypovolemia (which even in adequately resuscitated patients with extensive burns averages 20% of their predicted blood and plasma volumes) and depression of cardiac output cause reduction in blood flow to many tissues and organs [17]. This effect can be accentuated by both generalized and local increases in vascular resistance due to reflex vasoconstriction and can be exaggerated by the outpouring of catecholamines that occurs immediately postburn. The studies of Harjola and Silvula [18] and the more recent studies by Sales et al. [19], Hottenrot et al. [20], Ritchie [21], and Silen's group [22] confirm the importance of impaired gastric mucosal blood flow in the etiology of stress ulcer disease following hemorrhage. The impairment of mucosal blood flow due to hemorrhage appears to be uneven in distribution [18, 19], and this is entirely consistent with the focal nature of the early gastritic and duodenitic changes as previously described. The mechanisms postulated by the investigators as being responsible for mucosal damage secondary to ischemia include: increased sympathetic nervous activity; tissue hypoxia; increased susceptibility to the mucosal barrier breaking effects of bile salts resulting in increased acid back-diffusion; and mucosal acidosis.

Using 50μ radiolabeled microspheres gastric blood flow changes following burn injury were examined by Asch et al. [23] in a canine preparation with a 40% full-thickness burn. In that model no significant change in total gastric blood flow was identified at either 1 hour or 5 hours postburn despite a 35% decrease in cardiac output at the former time. Submucosal arteriovenous shunting in the gastric wall has been invoked as a possible explanation for such observations. Although such shunts have been identified, they are apparently of inadequate num-

ber to explain the general mucosal response to hypovolemia, and the low level of microsphere recovery in gastric venous blood does not support such a concept [19]. A more likely mechanism appears to be an alteration of mucosal blood flow in response to the neurohormonal changes consequent to injury, and such a mechanism is supported by the studies, largely using models of hemorrhagic shock, of several investigative groups [24-27].

Studies by Menguy and Masters [28] using rabbit and rat shock models suggest that even modest degrees of ischemia may product an energy deficit in the gastric mucosa manifested by a diminution of tissue ATP levels, a depletion of mucosal glycogen content, and an associated increase in AMP levels. The relative resistance of the antrum to mucosal injury appears to be explained by the finding that its blood flow and energy metabolism are better maintained in the presence of shock. Antral ATP levels, although initially lower than in the fundus or corpus, were maintained at relatively higher levels during ischemia, and "glycolytic flux" was less accelerated in the antral mucosa than in the mucosa of the fundus or corpus. The importance of energy supply in the genesis of gastroduodenal mucosal injury is further corroborated by the studies of Mullane et al. [29], showing an increase in gastric mucosal lesions in starved restrained rats as compared to fed restrained rats, and by studies at this Institute [30] using a rat burn model, showing that preburn adrenalectomy, preburn or postburn starvation, or postburn insulin administration increased the incidence of acute gastric ulcers as compared to that in animals which were fed before and/or after burn injury.

A precise role of bile salts and lysolecithin (which are known to be injurious to gastric mucosa) [31, 32] in the pathogenesis of Curling's ulcer has not been defined, but it should be noted that ileus is a common accompaniment of early postburn hypovolemia in patients with burns of more than 25% of the total body surface, and that intraluminal bile was noted in many of our patients at the time of initial endoscopic examination in the early postburn period. Ileus and duodenal regurgitation also commonly occur in association with sepsis later in the postburn period, and bile salts and lysolecithin contained in the duodenal fluid may account, at least in part, for the frequent occurrence of gastric mucosal disease in septic patients.

Lastly, the high concentrations of carbonic anhydrase present in both the oxyntic and surface cells of the gastric mucosa may exert a protective effect by facilitating surface cell bicarbonate secretion to neutralize acid or by enhancing carbonic acid dissociation to limit acid production [33]. Administration of inhibitors of carbonic anhydrase is associated with gastric mucosal ulceration in animal preparations. Although this is yet another potential factor in the pathogenesis of gastric mucosal injury in burn patients treated with mafenide acetate burn cream (a potent inhibitor of carbonic anhydrase), the clinical importance of this mechanism in the burn patient is questionable since no significant increase in the incidence of Curling's ulcers occurred following the institution of such topical therapy in the mid-1960's.

Prophylaxis

Many of the etiologic factors, when acting alone, do not appear capable of consistently producing gastroduodenal mucosal injury. The interactions of a variable number of these factors appear to define the balance of mucosal protective and destructive effects, and to determine the fate of the gastric and duodenal mucosa in terms of the occurrence and severity of cellular injury. Consequently, effective stress ulcer prophylaxis will commonly require institution of measures to enhance mucosal protective factors as well as measures effective against the one or more agents acting to injure the mucosa at any given time. The importance of the immediate postinjury impairment of gastric mucosal blood flow in the genesis of mucosal injury serves to emphasize the need to limit the deleterious hemodynamic and blood volume changes and gastric tissue acidosis in the severely burned patient by prompt administration of adequate volumes of resuscitation fluid in order to minimize the severity of mucosal injury. The endoscopic identification of gastritis and duodenitis at 5 hours postburn even in patients who are satisfactorily resuscitated suggests that some degree of mucosal injury occurs in virtually every severely burned patient. The goal of prophylaxis, then, becomes the prevention of progression of these precursor lesions to frank ulcerations and the clinical complications thereof, i.e., perforation and bleeding. Obvious prophylactic, and at times therapeutic, measures to prevent the development of stress ulcers and their complications include: early diagnosis and effective treatment of sepsis; ventilatory support as needed to prevent the development of respiratory acidosis which can, by vagal effect, increase gastric acid production; and provision of adequate calories to meet the accentuated metabolic needs of the burn patient, thereby ensuring an adequate energy supply to maintain integrity of uninjured gastric mucosa and permit repair of damaged mucosa.

The cardinal role played by gastric acid in the progression of acute mucosal disease indicates that reduction of the acidity of the gastric luminal con-

Table 4. Comparison of cimetidine and antacid stress ulcer prophylaxis in burn patients, determined endoscopically in a double-blind clinical trial.

	Cimetidine (400 mg q 4 hr)	Antacid (to maintain gastric content at pH 5.0 or above)
Total number of patients entered	20	20
Number of patients studied for 10 days	13	14
Positive endoscopic findings:		
Day of admission	4	4
Day 3	10	10
Day 10	4	11
Patients with clinical ulcer complications	0	0

tents should exert beneficial actions directly by reducing hydrogen ion concentration within the stomach, and secondarily by inhibiting the activation of pepsinogen. Since frank ulceration can occur as early as 96 hours postburn, measures to reduce the acidity of the gastric contents should be instituted during the resuscitation period, particularly during the period of ileus when the likelihood of significant bile reflux is greatest. A controlled trial by McAlhany et al. [34] demonstrated in 48 patients with burns of more than 35% of the total body surface that prophylactic antacid buffering significantly reduced the occurrence of the clinical complications of acute postburn gastroduodenal disease. Seven of the 24 patients who did not receive antacid prophylaxis experienced complications related to stress ulcer disease, hemorrhage in 6 and perforation in 1. Only 1 of the 24 patients receiving prophylactic antacids developed a similar complication. Hemorrhage occurred in the 1 patient in whom antacid administration was stopped because of metabolic alkalosis. The bleeding in that patient was controlled by reinstitution of antacid instillation. Even in those study patients having evidence of mucosal barrier disruption (as determined by the previously cited lithium flux technique), antacid prophylaxis significantly reduced the complications of postburn mucosal disease. No complications occurred in the 7 patients with evidence of a disrupted mucosal barrier who received antacid prophylaxis, while 6 complications occurred in 15 patients with evidence of a disrupted gastric mucosal barrier not receiving antacid prophylaxis.

As an alternative to acid buffering, the production of gastric acid can be strikingly reduced by the administration of the histamine H_2 receptor antagonist, cimetidine. This agent has been found in a series of studies by Levine, Sirinek, and associates [35] to prevent stress-induced gastric erosions in rats subjected to restraint and exposure to cold; to reduce the depression of gastric mucosal blood flow in a miniature swine shock model when administered either preshock or postshock [26, 35]; and to diminish postburn gastric edema in a rat model when administered either preburn or postburn [37]. A double-blind clinical comparison of the effectiveness of cimetidine (400 mg every 4 hours) and antacid for the prophylaxis of stress ulceration following burn injury has shown the 2 agents to provide equal protection [38]. Esophagogastroduodenoscopy was carried out on admission and at 3 and 10 days postadmission in the study patients. The incidence of mucosal abnormalities at the time of admission was similar in both groups, but by day 10 significantly fewer of the 13 cimetidine-treated patients still had mucosal abnormalities (Table 4). One patient in the cimetidine-treated group had numerous gastric pH values of less than 5.0, and even though his mucosa remained normal, he was changed to antacid prophylaxis following the initial 10 day study period. One patient receiving antacids developed metabolic alkalosis and colonic pseudoobstruction during the study. Significant side effects of cimetidine, such as mental obtundation, interstitial nephritis, and neutropenia, were not observed in our study patients and, in fact, ileus was less common in the cimetidine-treated group than in the antacid-treated group.

It should be noted that recent reports by Priebe et al. [39] and Martin et al. [40] have suggested that cimetidine prophylaxis is less effective than antacid prophylaxis in protecting seriously ill patients from acute gastrointestinal bleeding, but in both of those studies, endoscopic examination was not carried out, and the source of what was the usually modest bleeding remains uncertain. At the present time we prefer cimetidine prophylaxis because the agent can be given parenterally when ileus is present, and its use is not complicated by the formation of medication bezoars. The administration of cimetidine is begun on admission and is given in a dosage of 400 mg every 4 hours by the parenteral route until gastroin-

Table 5. Operative treatment of Curling's ulcer (1954-June 1980).

	No. of patients	Survived	Died
Vagotomy and antrectomy	39	10	29
Subtotal gastrectomy	21	8	13
Plication of ulcer	9	1	8
Vagotomy and pyloroplasty	6	2	5
Vagotomy and gastrojejunostomy*	2	2	0
Total	77	22	55

*Performed in 2 patients with ulceration and superior mesenteric artery syndrome causing partial duodenal obstruction.

testinal motility returns. At that time the dosage is changed to 300 mg by the oral route every 4-6 hours until the burns have healed in the case of second degree injury, or have been reduced to less than 35% of the total body surface by grafting in the case of full-thickness injuries. The occurrence of metabolic alkalosis, the reduced effectiveness of antacid prophylaxis in the presence of ileus, and the formation of medication bezoars, which may cause intestinal obstruction requiring surgical relief [41], limit the use of antacids for stress ulcer prophylaxis. Nevertheless, antacid should be used for stress ulcer prophylaxis and cimetidine avoided in patients with evidence of hepatic or renal failure, patients receiving anticoagulant therapy, and patients with neutropenia. The antacid should be instilled through the nasogastric tube in sufficient volume to keep the pH of the gastric contents above 5.0, as assessed by hourly monitoring. Additionally, we do not hesitate to administer antacids and continue cimetidine prophylaxis to any patient in whom the latter by itself fails to maintain the pH of the intraluminal contents above 5.0.

The use of these prophylactic measures has reduced the incidence of bleeding and perforation in our entire burn patient population to 3% in 1976, 2% in 1977, 1% in 1978, and 1% in 1979. No instance of hemorrhage requiring operative control occurred during that period. In the present calendar year, 1 patient, in whom antacid prophylaxis was prematurely terminated, required operation for closure of a perforated ulcer.

In recent years, as the incidence of upper gastrointestinal tract stress ulceration has decreased as a result of effective prophylaxis, it has become apparent that more distal portions of the bowel, particularly the colon, are also susceptible to stress ulcer formation in burn patients with severe complications. Acute ulcers of the colon have been identified both clinically and at autopsy in those burn patients with severe sepsis, particularly those experiencing hypotension. The histologic characteristics of these lesions resemble those of Curling's ulcer with little edema or inflammatory change, but are characteristically heavily colonized by the abundant bacterial population of the colonic contents. Although most of the lesions are superficial in character, some have extended to the serosa. As yet, no free perforations of the colon have been observed. If the underlying condition is corrected, the more superficial ulcers of the large bowel may undergo healing as indicated by distortion of the colonic wall architecture in tissue samples harvested at autopsy.

Treatment of Clinical Complications of Stress Ulcer Disease in Burn Patients

If prophylaxis fails and significant bleeding occurs, various authors recommend intragastric irrigation with warm saline [42] and/or selective arterial injection of vasoactive agents such as posterior pituitary extract [43] (the potential beneficial effects of such agents in reducing the rate of bleeding must be balanced against their ability to impair mucosal blood supply and thereby accentuate mucosal damage). Recent reports have indicated that parenteral infusion of somatostatin is effective in controlling bleeding from acute ulcers that have been unresponsive to cimetidine [44]. The number of patients treated with that agent has been small, and a controlled study will be needed to confirm its effectiveness. Time should not be wasted by inappropriately prolonged use of ineffective nonoperative treatment, since continued hemorrhage may precipitate profound pathophysiologic changes and increase mortality in an already critically ill burned patient who was in precarious physiologic and metabolic balance prior to the onset of bleeding.

The indications for operative intervention in 77 patients during the past 26½ years have been: massive bleeding uncontrollable by nonoperative means or of sufficient magnitude as to require replacement of more than 2500 ml of blood over a 12-hour period in 53 patients; bleeding of lesser magnitude for over 48 hours in 8 patients; and perforation in 16 patients. In the burned child, when total blood replacement for prolonged bleeding from a stress ul-

cer approaches 60% of estimated blood volume, operative intervention should be entertained [6, 45]. The critical condition of those patients requiring surgery and the frequency of coexisting sepsis demand as limited an operative procedure as is consistent with adequate treatment. Although nonresectional surgery is inherently attractive, our results in a small number of patients so treated have been disappointing. In 17 patients who underwent nonresectional surgical treatment, massive rebleeding occurred in 2 and suture line disruption in 1. The previously noted observation of subsequent ulcer formation in a patient who underwent simple closure of a perforated ulcer suggests that nonresectional therapy may be inadequate treatment even for perforated ulcers in these critically ill patients. Resection is contraindicated in the presence of intra-abdominal sepsis such as lesser sac abscess formation secondary to perforation of an acute posterior wall ulcer; the abscess must of course be drained.

Our operative experience reveals that similar results have been obtained with both subtotal gastrectomy and with antrectomy combined with vagotomy (Table 5). We prefer the latter procedure to take advantage of the beneficial effects of vagotomy on the gastric mucosal blood supply, and to eliminate the effect of the vagus on acid secretion due to elevated carbon dioxide levels that may occur as a consequence of pulmonary complications. In any case, a generous gastrotomy incision must be made at the time of operation, since the multiplicity of ulcers and their frequent occurrence in both the duodenum and stomach make a thorough inspection of the entire mucosa mandatory. The goal of the resection portion of the operation is to remove the offending ulcer if at all possible, while preserving the maximum amount of gastric mass, since following healing or grafting of the burns, these patients have no greater risk of subsequent ulcer development than the population at large. Nevertheless, the resection may need to be extended beyond the level of the antrum to encompass the ulcer even if vagotomy then needs to be omitted. Fundic lesions that are a source of bleeding may be excised by wedge resection following which vagotomy and antrectomy are carried out. Rebleeding has occurred in only 4 of the 60 patients undergoing resection. In those patients, the source of bleeding included a duodenal ulcer which was overlooked and unexcised at the time of surgery, suture line disruption, or postoperative peritonitis.

The heavy bacterial density of the burn wound, the frequency of infections in other organs, and the frequent existence of nutritional and metabolic deficits in burn patients requiring operation for the complications of Curling's ulcers combine to cause a markedly high rate of postoperative wound infection. Retention sutures should be used in closing the operative wound. The skin and subcutaneous tissues should be left unsutured, covered with a biologic dressing or loosely packed open, and closed secondarily when one can be more confident that a wound infection will not develop.

Twenty-two of the 77 patients requiring operation survived both the surgery and their burn injuries and were discharged from the hospital. Ten of the patients who died following surgical intervention had resumed alimentation, and the cause of death in those patients was related to some other complication of their burn injury. When combined, these 2 groups represent a potential salvage rate of 42% in the patients undergoing surgery for a complication of stress ulceration, compared to an overall survival rate of only 23% in the entire group of burned patients with documented stress ulcerations. The improvement in survival following surgery for stress ulcer complications indicates that operative intervention should in no way be considered radical therapy, but instead should be considered mandatory treatment for the life-threatening complications of uncontrollable hemorrhage or perforation.

Résumé

Les ulcères de stress qui se développent dans l'estomac et le duodénum des brûlés graves (ulcères de Curling) sont dus à un défaut du mécanisme de défense de la muqueuse contre l'acide secrété. Ce défaut est lui-même dépendant, en partie en tout cas, de l'ischémie muqueuse qui est aggravée par l'hypotension, l'infection et l'hypoxie. L'administration prophylactique précoce d'antiacides et de cimétidine, seuls ou combinés, a réduit de façon significative la fréquence des complications graves de ces ulcérations. Si les thérapeutiques préventives échouent, ou si elles n'ont pas été utilisées, et si une hémorragie importante ou une perforation survient, le meilleur traitement est la gastrectomie avec vagotomie.

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Invited Commentary

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There have been suggestions in the past that the complicated ulcers developing in burn patients are a unique phenomenon related to the burn injury itself. This article builds a strong case to support the opinion that such is not the case. In all probability ulcerations of the upper gastrointestinal tract seen in burned patients are due to the same mechanisms responsible for upper gastrointestinal ulcerations in otherwise stressed and injured patients. The magnitude of the stress following a major burn and the relatively high incidence of sepsis in these patients probably account for the perceived difference in incidence.

The incidence of stress ulcers, at least as they are manifested by their complications, has dramatically decreased in burn units and other intensive care units throughout the country [1]. The increased overall survival rate and duration of survival of patients with large burns might lead one to expect an increase in the incidence of gastrointestinal ulcers, since there is a clearly demonstrated relationship between ulcers and the magnitude of the burn. As already mentioned, the opposite is occurring. Several factors undoubtedly contribute to this decline but no single one has been identified as the cause.

As mentioned in the article, improved immediate resuscitation should be beneficial in decreasing the incidence of superficial mucosal ulcerations. While there have been significant improvements in resuscitation over the last 20 years, there has been little substantial change in the last 5 to 10 years, the time period during which a decrease in stress ulcer incidence has been seen. In contrast, there have been at least 2 important advances occurring in this same time period. The first was realization of the importance of nutritional support in all stressed patients. Maintenance of reasonable nitrogen balance has considerably decreased the stress response in these patients. The second factor was the observation that, although stressed patients do not routinely secrete abnormal amounts of acid, the incidence of gastrointestinal bleeding was diminished by routine prophylactic antacid administration [2]. This observation led to routine pH monitoring and the hourly use of antacids to maintain gastric pH above 4.0. Increased use of continuous enteral tube feedings accomplished both goals—pH maintenance and nutritional support. During the same time period that these modalities came into common usage, the incidence of clinically significant stress ulcers has markedly decreased. In the past 3 years 811 patients were admitted to the University of Washington Burn Center and there has been only 1 death related to stress ulceration. The patient who died was a young male transferred to us 3 weeks postburn having had neither antacid nor nutritional support. On the day of admission, he suddenly vomited blood, aspirated, and died. There have been no cases of perforation, obstruction, or gastrointestinal bleeding significant enough to require operation in these burned patients.

While much progress has been made in this area, many questions remain unanswered. Specifically, 2 of the "therapeutic" points raised by the authors deserve further comment. The first involves methods for the protection of the stomach against acid. Several reports [3–5] have suggested that antacids are more effective than cimetidine in controlling gastric pH. This is particularly true in septic patients. In fact, control of gastric pH can be obtained more reliably by the use of antacids and careful monitoring. The authors imply, based on endoscopic evaluation of patients, that while cimetidine may provide less reliable control of pH, it has other effects that make it equivalent to antacids in pre-

vention of gastric mucosal ulcerations. Uniform agreement on this point has not yet been reached. The suggestion that a higher incidence of complications is encountered by the use of antacids was not borne out by other investigators using antacids and cimetidine in a controlled prospective study [5]. Whatever the eventual answer to this problem, it seems reasonable at this point to recommend monitoring of gastric pH regardless of the agents being used to control it. This is particularly likely to be of benefit to patients who are septic.

The second point that deserves comment is the recommendation for resectional surgery in the rare individual who requires surgical intervention. The supporting data are suggestive but not extensive, and the above recommendation is not uniformly accepted. We agree that resection (antrectomy and vagotomy) is appropriate for discrete ulcers or multiple ulcers confined to one portion of the stomach or duodenum. On the other hand, for individuals with diffuse gastric erosions we still employ vagotomy and drainage. Whatever approach is taken, the outcome in these patients is less satisfactory than in those with discrete disease.

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Invited Commentary

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This article extensively reviews the pathophysiology and clinical presentation of stress ulcer disease in the burned patient. Furthermore, the authors have clearly defined a prophylactic treatment protocol which should insure a very low incidence of this complication in severely burned patients. It should be emphasized that the authors have properly recognized the absence of abdominal pain following perforation of stress ulcers in burn patients. The diagnosis of perforation is most frequently confirmed by an upright x-ray study of the abdomen, which will reveal the presence of free air. The absence of a "boardlike" abdomen, tenderness, and involuntary guarding is not unusual. Presumably, these patients are unable to respond with a pronounced inflammatory reaction within the peritoneal cavity following perforation, perhaps as a result of the markedly increased elaboration of endogenous steroids secondary to the stress.

While the authors suggest that disruption of the gastric mucosal barrier with increased back-diffusion of hydrogen ion is not necessary for the development of early postinjury gastritic changes, increased back-diffusion of hydrogen ion in the presence of poor gastric perfusion is frequently associated with progression of gastritis to frank ulceration. Most investigators in this field now believe that tissue ischemia, increased back-diffusion of hydrogen ion, and mucosal acidosis each play a role in the development of stress ulceration, and that these mechanisms are interrelated and synergistic. The authors of this paper properly emphasize the requirement for prompt fluid resuscitation to prevent hypovolemia and hypotension during the early postburn period, in order to prevent prolonged gastric tissue acidosis and hypoxia.

There is no question that the incidence of stress ulceration has been markedly reduced during the past decade. A review of the last 1000 burned patients admitted to the New York Hospital Burn Center revealed that only 2 patients required operative intervention for stress ulceration. One was admitted 3 weeks postburn from another institution, at a time when he was clinically septic with burn wound infection; in addition to ulceration the patient had evidence of extensive disseminated intravascular coagulation as a complication of his sepsis. The second patient had a punched out ulcer on the lesser curvature; at the time of operation the perforation appeared to have been mechanically induced by the introduction of a large nasogastric tube for evacuation of blood clots, which apparently perforated a thinned out, ulcerated area in the fundus of the stomach. Thus, the incidence of severe gastrointestinal complications requiring oper-

ative intervention during the past 3 years has been less than 0.5% in a population of patients with an average burn size of 23% of the total body surface.

The decreased incidence of stress gastritis proceeding to frank stress ulceration is related to at least 4 factors. Firstly, better understanding of the resuscitation volume requirements following burn injury has served to minimize the period of time in which diminished perfusion of the gastric mucosa is present. Secondly, prophylactic utilization of antacids has allowed sufficient buffering of hydrogen ions within the stomach to prevent extensive back-diffusion. Clearly, the most common complication of antacid administration is metabolic alkalosis so that such patients should be carefully monitored for acid-base balance and electrolyte concentration. Thirdly, improved monitoring and prophylactic treatment of the burn wound with regard to bacterial colonization has significantly reduced the incidence of burn wound sepsis in patients with more than 20% total body surface burn. Pruitt has previously suggested that gastric ulceration was associated with sepsis in 75-85% of patients requiring operative intervention for gastrointestinal ulceration. In our Burn Center, pulmonary insufficiency, as a result of smoke inhalation or late bronchopneumonia, has replaced infection of the burn wound as the principle cause of death. The overall incidence of septic complications has been progressively reduced and this has been associated with a simultaneous reduction in the incidence of gastrointestinal complications. Finally, it is important to point out that nutritional maintenance of the hypermetabolic burn patient has been markedly improved during the past decade. More accurate provision of caloric requirements during the early postburn period is associated with absence of significant weight loss during hospitalization. It has long been known that wound healing is very sensitive to energy balance, and the provision of adequate calories would be expected to improve the mucosa proliferative index in patients with early, nonconfluent gastric lesions.

We have preferred to treat patients with antacids alone prophylactically during the early postburn period. The dose of antacids can be adjusted to maintain the gastric pH above 5.0. Should obstipation or diarrhea occur, the specific formulation of the antacids may be altered to alleviate the symptoms. When metabolic alkalosis is induced, it may be easily corrected by discontinuing the antacids and substituting cimetidine administration. We have reserved use of cimetidine for patients who develop gastrointestinal bleeding despite antacid prophylaxis. In such cases, cimetidine is administered and the patient is carefully monitored. In our experience, it is advisable to use both cimetidine and antacid prophylaxis in patients with major burn injuries and a previous history of peptic ulcer disease, previous gastrointestinal hemorrhage, or clinically significant portal hypertension.

When operative intervention is required, vagotomy and antrectomy is the procedure of choice. Usually such patients have septic complications and the incidence of rebleeding with lesser operations is unacceptably high. Furthermore, such patients rarely tolerate sequential operations so that the most definitive acid-reducing procedure should be done at the time of the initial exploration.

In summary, the incidence of stress ulceration in burn patients has been markedly reduced in burn centers across the nation. The incidence of significant gastrointestinal bleeding is less than 1% in severely burned patients, provided the patient has been appropriately resuscitated, prophylactically treated with antacids or antihistamines, protected against bacterial burn wound colonization, and adequately supported by exogenous nutritional replenishment.